

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To: BAKER, Suzanne GLAXOSMITHKLINE C.I.P. (CN925.1) 980 Great West Road Brentford Middlesex TW8 9GS GRANDE BRETAGNE	GlaxoSmithKline Corporate IP Received BRENTFORD 04 AUG 2005	NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (PCT Rule 71.1)
ATTY. <i>SJB</i> IPM <input checked="" type="checkbox"/> N/A <input type="checkbox"/> ON <input type="checkbox"/> UPDATED ON: <i>02</i> ATTY CHECKED <i>02</i>		Date of mailing (day/month/year) 02.08.2005

Applicant's or agent's file reference SJB-PB60266/PCT		IMPORTANT NOTIFICATION
International application No. PCT/EP2004/006591	International filing date (day/month/year) 17.06.2004	Priority date (day/month/year) 19.06.2003
Applicant GLAXO GROUP LIMITED et al.		

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.



4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Siefert, A Tel. +49 89 2399-2469	
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SJB-PB60266/PCT	FOR FURTHER ACTION		See Form PCT/IPEA416
International application No. PCT/EP2004/006591	International filing date (day/month/year) 17.06.2004	Priority date (day/month/year) 19.06.2003	
International Patent Classification (IPC) or national classification and IPC A61K31/4025, A61K31/4015, C07D207/26, C07D409/12, C07D409/14, A61P7/00			
Applicant GLAXO GROUP LIMITED et al.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input checked="" type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 09.12.2004		Date of completion of this report 02.08.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Bérillon, L Telephone No. +49 89 2399-7078 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

 International application No.
PCT/EP2004/006591

IAP20 Rec'd PCT/EP 19 DEC 2005

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-49 as originally filed

Claims, Numbers

1-13 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/006591

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:
- see separate sheet**

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 12
- because:
- ☒ the said international application, or the said claims Nos. 12 relate to the following subject matter which does not require an international preliminary examination (specify):
- see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.
 - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
 - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
 - ☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/006591

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-13
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-13
Industrial applicability (IA)	Yes: Claims	1-11,13
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

PCT/EP2004/006591

IAP20 Rec'd PCT/PTO 19 DEC 2005**Re Item II****Priority**

The claimed priority is valid. Hence the P-document cited in the ISR is not considered as relevant prior art.

Re Item III**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 12 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1 Prior art**

Reference is made to the following documents:

D1: WO 98/24784
D2: WO 01/39759
D3: WO 03/043981

2 Novelty (Article 33(2) PCT)

- 2.1 The present compounds differ from those disclosed in D1 in view of their amide group -CON(R3)-.
- 2.2 The present compounds differ from those disclosed in D2 and D3 in view of their group X directly bound to the nitrogen atom of the pyrrolidone ring.

3 Inventive step (Article 33(3) PCT)

The closest prior art is represented by D1.

The technical problem underlying the present application is regarded as the provision of further compounds useful as factor Xa inhibitors. Said problem has been allegedly solved by the present compounds of formula (I). For the purpose of assessing inventive step during the International Preliminary Examination it is assumed that these compounds indeed are factor Xa inhibitors i.e. solve the above defined technical problem.

D1 discloses compounds having said activity and which are structurally related to the present compounds of formula (I): they differ only in respect of the definitions of substituents X_5 and X_{5a} (see D1, claim 1, formula I with n is 1, m is 1, X_2 and X_{2a} form oxo and A is S). Said substituents X_5 and X_{5a} taken together are =NR5 whereas in the present compounds an oxo group is present in this position. It is noted however, that D2 discloses compounds having an oxo group in this position (see D2, claim 1 with X_5 is $R_5 R_6 NCO-$). Accordingly, the skilled person aware of D1 and D2 would have reached the present compounds by combining said documents D1 and D2 without the exercise of inventive step.

It is acknowledged that there is no examples provided in D1 where $n = 0$ i.e. where the pyrrolidine ring is directly bound to ring Ar1 (see D1, claim 1) as in the present compounds. It is however maintained that since claim 1 encompasses compounds where $n = 0$, there is a clear teaching for the skilled person that those compounds of D1, claim 1 where the pyrrolidine ring is directly bound to ring Ar1 do solve the posed technical problem.

Inventive step could only be acknowledged if the present compounds were shown to exhibit unexpected properties (i.e. to solve unexpectedly a problem not yet solved) when compared to the structurally closest related compounds according to D1.

4 Industrial applicability (Article 33(4) PCT)

For the assessment of present claim 12 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known com-

pound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

The present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The functional term "pharmaceutically acceptable derivative thereof" does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of said claims.